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Application No. <u>09/780,608</u>	Prepared by <u>DLP</u>		Tracking Number <u>060/3004</u>	
Examiner-GAU <u>Saunders - 16044</u>	Date <u>10/27/04</u>		Week Date <u>9/20/04</u>	
	No. of queries <u>1</u>		1FW(PUR)	

JACKET

a. Serial No.	f. Foreign Priority	k. Print Claim(s)	<input checked="" type="checkbox"/> PTO-1449
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SPECIFICATION

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FORM PTO - 1449

SECOND SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT

ATTORNEY DOCKET NO.: LEX-011

APPLICANT(S): Gillies *et al.*

SERIAL NO.: 09/780,668

EXAMINER: David A. Saunders

FILING DATE: February 9, 2001 GROUP: 1644

U.S. PATENT DOCUMENTS

EXAM. INIT.		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE
	A60	4,703,008	10/27/87	Lin	435	240.2	11/30/84
	A61	5,457,038	10/10/95	Trinchieri <i>et al.</i>	435	69.52	9/18/90
	A62	5,441,868	8/15/95	Lin	435	69.4	10/23/87
	A63	5,547,933	8/20/96	Lin	514	8	6/7/95
	A64	5,618,698	4/8/97	Lin	435	69.4	6/6/95
	A65	5,650,150	7/22/97	Gillies	424	134.1	7/27/94
	A66	5,688,679	11/18/97	Powell	435	240.2	10/6/93
	A67	5,723,125	3/3/98	Chang <i>et al.</i>	424	134.1	9/25/96
	A68	5,756,349	5/26/98	Lin	435	325	6/6/95
	A69	5,908,626	6/1/99	Chang <i>et al.</i>	424	134.1	12/19/97
	A70	5,955,422	9/21/99	Lin	514	8	8/2/93
	A71	6,100,387	8/8/00	Herrmann <i>et al.</i>	536	23.4	2/28/97
	A72	6,231,536	5/15/01	Lentz	604	5.04	5/21/99
	A73	6,284,536	9/4/01	Morrison <i>et al.</i>	435	328	4/20/99
	A74	6,335,176 B1	1/1/02	Inglese <i>et al.</i>	435	7.72	10/16/98
	A75	6,340,742	1/22/02	Burg <i>et al.</i>	530	351	6/28/00
	A76	6,444,792	9/3/02	Gray <i>et al.</i>	530	387.3	1/8/99
	A77	6,475,717 B1	11/5/02	Enssle <i>et al.</i>	435	5	7/25/97
	A78	6,485,726 B1	11/26/02	Blumberg <i>et al.</i>	424	178.1	7/24/98
	A79	6,506,405	1/14/03	Desai <i>et al.</i>	424	450	8/1/00
	A80	6,583,272	6/24/03	Bailon	530	397	6/27/00
	A81	6,586,398	7/1/03	Kinstler <i>et al.</i>	514	12	4/7/00
	A82	6,617,135	9/9/03	Gillies <i>et al.</i>	435	69.7	8/9/00
	A83	2001/0053539 A1	12/20/01	Lauffer <i>et al.</i>	435	69.1	4/6/99

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	A84	2002/0081664 A1	6/27/02	Lo <i>et al.</i>	435	69.5	10/11/01
	A85	2002/0142374 A1	10/3/02	Gallo <i>et al.</i>	435	69.1	8/17/99
	A86	2002/0147311 A1	10/10/02	Gillies <i>et al.</i>	530	387.1	2/9/01
	A87	2002/0192222 A1	12/19/02	Blumberg <i>et al.</i>	424	178.1	8/8/02
	A88	2002/0193570 A1	12/19/02	Gillies <i>et al.</i>	530	351	12/4/01
	A89	2003/0003529 A1	1/2/03	Bayer	435	68.1	7/19/02
	A90	2003/0044423 A1	3/6/03	Gillies <i>et al.</i>	424	192.1	3/7/02
	A91	2003/0049227 A1	3/13/03	Gillies <i>et al.</i>	424	85.1	6/29/01
	A92	2003/0105294 A1	6/5/03	Gillies <i>et al.</i>	530	351	2/24/99
	A93	2003/0012789 A1	1/6/03	Blumberg <i>et al.</i>	424	145.1	8/8/02
	A94	2003/0157054 A1	8/21/03	Gillies <i>et al.</i>	424	85.1	5/3/02
	A95	2003/0166163 A1	9/4/03	Gillies	435	69.52	12/4/02
	A96	2003/0166877 A1	9/4/03	Gillies <i>et al.</i>	530	395	3/29/02

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FOREIGN PATENT DOCUMENTS

EXAM INIT.	DOCUMENT NUMBER	DATE	COUNTRY CODE	CLASS	SUB CLASS	FILING DATE	ABSTRACT ONLY	ENGLISH LANG (Y/N)
	B92 1088 888 A1	4/04/01	EP			5/13/99	N	Y
	B93 WO 96/18412	6/20/96	PCT			12/12/94	N	Y
	B94 WO 97/00319	1/03/97	PCT			6/11/96	N	Y
	B95 WO 99/43713	9/02/99	PCT			2/24/99	N	Y
	B96 WO 00/24893	5/04/00	PCT			10/18/99	N	
	B97 WO 01/36489 A2	5/25/01	PCT			11/03/00	N	Y
	B98 WO 01/58957 A2	8/16/01	PCT			2/09/01	N	Y
	B99 WO 02/02143 A2	1/10/02	PCT			06/29/01	N	Y
	B100 WO 02/066514 A2	8/29/02	PCT			2/18/02	Y	Y
	B101 WO 02/072605 A2	9/19/02	PCT			3/07/02	N	Y
	B102 WO 02/079232 A2	10/10/02	PCT			3/30/02	N	Y
	B103 WO 02/079415 A2	10/10/02	PCT			3/29/02	N	Y
	B104 WO 02/090566 A2	11/14/02	PCT			5/03/02	N	Y
	B105 WO 03/048334 A2	6/12/03	PCT			12/04/02	N	Y
	B106 WO 03/077834 A2	9/25/03	PCT			7/03/02	N	Y

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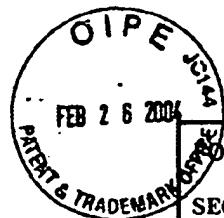
EXAMINER: David A. Saunders

FILING DATE: February 9, 2001 GROUP: 1644

EXAM. INIT.	OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)
C171	Angal <i>et al.</i> , (1993), "A Single Amino Acid Substitution Abolishes the Heterogeneity of Chimeric Mouse/Human (IgG4) Antibody," <u>Molecular Immunology</u> , 30:105-108.
C172	Batova <i>et al.</i> , (1999), "The Ch 14.18-GM-CSF Fusion Protein Is Effective at Mediating Antibody-dependent Cellular Cytotoxicity and Complement-dependent Cytotoxicity in Vitro," <u>Clinical Cancer Research</u> , 5:4259-4263.
C173	Becker <i>et al.</i> , (1996), "Long-lived and transferable tumor immunity in mice after targeted interleukin-2 therapy," <u>J Clin Invest.</u> , 98(12):2801-4.
C174	Becker <i>et al.</i> , (1996), "T Cell-mediated eradication of murine metastatic melanoma induced by targeted interleukin 2 therapy," <u>J Exp Med.</u> , 183(50):2361-6.
C175	Bitonti <i>et al.</i> , (2002), "Transepithelial Absorption of an Erythropoietin-Fc Fusion Protein After Delivery to the Central Airways," <u>Respiratory Drug Delivery</u> , 8:309-312.
C176	Briggs <i>et al.</i> , (1974), "Hepatic Clearance of Intact and desialylated Erythropoietin," <u>American Journal of Physiology</u> , 227:1385-1388.
C177	Chuang <i>et al.</i> , (1994), "Alteration of Lymphocyte Microtubule Assembly, Cytotoxicity, and Activation by the Anticancer Drug Taxol," <u>Cancer Research</u> , 54:1286-1291.
C178	Cruse <i>et al.</i> , (1995), <u>Illustrated Dictionary of Immunology</u> , CRC Press, NY, p.156-7.
C179	Darling <i>et al.</i> , (2002), "Glycosylation of Erythropoietin Affects Receptor Binding Kinetics: Role of Electrostatic Interactions," <u>Biochemistry</u> , 41:14524-14531.
C180	Davis <i>et al.</i> , (2003), "Immunocytokines: amplification of anti-cancer immunity," <u>Cancer Immunol Immunother</u> 52:297-308
C181	Dolman <i>et al.</i> , (1998), "Suppression of human prostate carcinoma metastases in severe combined immunodeficient mice by interleukin 2 immunocytokine therapy," <u>Clin Cancer Res.</u> , 4(10):2531-7.
C182	Duncan <i>et al.</i> , (1988), "The binding site for C1q on IgG," <u>Nature</u> , 332:738-740.
C183	Egrie <i>et al.</i> , (2001), "Development and characterization of novel erythropoiesis stimulating protein (NESP)," <u>Nephrol. Dial. Transplant.</u> , 16:3-13.
C184	Elliott <i>et al.</i> , (1997), "Mapping of the Active Site of Recombinant Human Erythropoietin," <u>Blood</u> , 89(2):493-502.
C185	Fell <i>et al.</i> , (1991), "Genetic Construction and Characterization of Fusion Protein Consisting of a Chimeric F(ab') with Specificity for Carcinomas and Human IL-2," <u>The J. of Immunology</u> , 146:7:2446-2452.

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C186	Fibi <i>et al.</i> , (1995), "N- and O-Glycosylation Muteins of Recombinant Human Erythropoietin Secreted From BHK-21 Cells," <u>Blood</u> , 85:1229-1236.
C187	Frost <i>et al.</i> , (1997), " A Phase I/II Trial of Murine Monoclonal Anti-GD2 Antibody 14.G2a plus Interlukin-2 Children with Refractory Neuroblastoma", <u>Cancer</u> , 80:317-33.
C188	Gan <i>et al.</i> , (1999), "Specific enzyme-linked immunosorbent assays for quantitation of antibody-cytokine fusion proteins," <u>Clin Diagn Lab Immunol.</u> , 6(2):236-42.
C189	Gillies <i>et al.</i> , (1991), "Expression of genetically engineered immunoconjugates of lymphotoxin and a chimeric anti-ganglioside GD2 antibody," <u>Hybridoma</u> , 10(3):347-56.
C190	Gillies <i>et al.</i> , (1999), "Improving the Efficacy of Antibody-Interleukin 2 Fusion Proteins by Reducing Their Interaction with Fc Receptors," <u>Cancer Research</u> , 59:2159-2166.
C191	Gillies <i>et al.</i> , (2002), "Bi-functional cytokine fusion proteins for gene therapy and antibody-targeted treatment of cancer," <u>Cancer Immunol Immunother.</u> , 51(8):449-60.
C192	Gillies <i>et al.</i> , (2002), "Improved circulating half-life and efficacy of an antibody-interleukin 2 immunocytokine based on reduced intracellular proteolysis," <u>Clin. Cancer Res.</u> , 8(1):210-6.
C193	Greene <i>et al.</i> , (1975), "Neuronal properties of hybrid neuroblastoma X sympathetic ganglion cells", <u>Proc. Natl. Acad. Sci. USA</u> , 72:4923-4927.
C194	Hammerling <i>et al.</i> , (1996), "In vitro bioassay for human erythropoietin based on proliferative stimulation of an erythroid cell line and analysis of carbohydrate-dependent microheterogeneity," <u>Journal of Pharmaceutical and Biomedical Analysis</u> , 14:1455-1469.
C195	Hank <i>et al.</i> , (2003), "Determination of peak serum levels and immune response to the humanized anti-ganglioside antibody-interleukin-2 immunocytokine," <u>Methods Mol Med.</u> , 85:123-31.
C196	Haraguchi, (1994), " Isolation of GD3 synthase gene by expression cloning of GM3 α -2,8-sialyltransferase cDNA using anti-GD2 monoclonal antibody, <u>Proc. Natl. Acad. Sci. USA</u> , 91(22):10455-9.
C197	Harris, (1995), "Processing of C-terminal lysine and arginine residues of proteins isolated from mammalian cell culture," <u>J. Chromatogr. A.</u> , 705:129-134.
C198	Hezareh <i>et al.</i> , (2001), "Effector function activities of a panel of mutants of a broadly neutralizing antibody against human immunodeficiency virus type 1," <u>J. Virol.</u> , 75(24):12161-8.
C199	Idusogie <i>et al.</i> , (2000), "Mapping of the C1q binding site on rituxan, a chimeric antibody with a human IgG1 Fc," <u>J. Immunol.</u> , 164(8):4178-84.
C200	Imboden <i>et al.</i> , (2001), "The level of MHC class I expression on murine adenocarcinoma can change the antitumor effector mechanism of immunocytokine therapy," <u>Cancer Res.</u> , 61(4):1500-7.

EXAMINER

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C201	Kato <i>et al.</i> , (1997), "Mechanism for the Nonlinear Pharmacokinetics of Erythropoietin in Rats," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 283:520-527.
C203	Kato <i>et al.</i> , (1998), "Pharmacokinetics of Erythropoietin in Genetically Anemic Mice," <u>Drug Metabolism and Disposition</u> , 26:126-131.
C204	Kendra <i>et al.</i> , (1999), "Pharmacokinetics and Stability of the ch 14.18-Interleukin-2 Fusion Protein in Mice," <u>Cancer Immunol. Immunotherapy</u> , 48:219-229.
C205	King <i>et al.</i> , (2003), "A Phase I/II clinical trial of the immunocytokine hu14.18-IL2 (EMD 273063) in patients with melanoma," Author's manuscript dated June 6, 2003.
C206	Kitamura <i>et al.</i> , (1989), "Establishment and Characterization of a Unique Human Cell Line that Proliferates Dependently on GM-CSF, IL-3, or Erythropoietin," <u>Journal of Cellular Physiology</u> , 140:323-334.
C207	Kushner <i>et al.</i> , (2001), "Phase II Trial of the Anti-GD2 Monoclonal Antibody 3F8 and Granulocyte-Macrophage Colony-Stimulating Factor for Neuroblastoma". <u>J. Clin. Oncol.</u> , 19:4189-94.
C208	Locatelli <i>et al.</i> , (2001), "Darbepoetin alfa Amgen," <u>Current Opinion in Investigational Drugs</u> , 2:1097-1104.
C209	Lode <i>et al.</i> , (1997), "Targeted interleukin-2 therapy for spontaneous neuroblastoma metastases to bone marrow," <u>J Natl Cancer Inst.</u> , 89(21):1586-94.
C210	Lode <i>et al.</i> , (2000), "What to do with targeted IL-2," <u>Drugs Today</u> , 36(5):321-36.
C211	Lode <i>et al.</i> , (2000), "Melanoma immunotherapy by targeted IL-2 depends on CD4(+) T-cell help mediated by CD40/CD40L interaction," <u>J. Clin. Invest.</u> , 105(11):1623-30.
C212	Macdougall, (2002), "Optimizing the Use of Erythropoietic Agents—Pharmacokinetic and Pharmacodynamic Considerations," <u>Nephrol. Dial. Transplant.</u> , 17:66-70.
C213	Metelitsa <i>et al.</i> , (2002), "Antidisialoganglioside/granulocyte macrophage-colony-stimulating factor fusion protein facilitates neutrophil antibody-dependent cellular cytotoxicity and depends on Fc gamma RII (CD32) and Mac-1 (CD11b/CD18) for enhanced effector cell adhesion and azurophil granule exocytosis," <u>Blood</u> , 99(11):4166-73.
C214	Mueller <i>et al.</i> , (1997), "Humanized porcine VCAM-specific monoclonal antibodies with chimeric IgG2/G4 constant regions block human leukocyte binding to porcine endothelial cells," <u>Molecular Immunology</u> , 34(6):441-452.
C215	Mullins <i>et al.</i> , (1997), "Taxol-mediated changes in fibrosarcoma-induced immune cell function: modulation of antitumor activities," <u>Cancer Immunol. Immunother.</u> , 45:20-28.
C216	Naramura <i>et al.</i> , "Mechanisms of cellular cytotoxicity mediated by a recombinant antibody-IL2 fusion protein against human melanoma cells," <u>Immunol. Lett.</u> , 39(1):91-9.

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FORM PTO - 1449 SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT		ATTORNEY DOCKET NO.: LEX-011 APPLICANT(S): Gillies <i>et al.</i> SERIAL NO.: 09/780,668 EXAMINER: David A. Saunders FILING DATE: February 9, 2001 GROUP: 1644
EXAM. INIT.	OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)	
C217	Neal et al., (2003), "NXS2 murine neuroblastomas express increased levels of MHC class I antigens upon recurrence following NK-dependent immunotherapy," <u>Cancer Immunol Immunother.</u> , Pub. Med ID: 14504825.	
C218	Ngo et al., (1994), "Computational Complexity, Protein Structure Prediction, and the Levinthal Paradox" pp. 433-440 and 492-495.	
C219	Niethammer et al., (2001) "An oral DNA vaccine against human carcinoembryonic antigen (CEA) prevent growth and dissemination of Lewis Lung carcinoma in CEA transgenic mice," <u>Vaccine</u> , 20(3-4):421-9.	
C220	Niethammer et al., (2001) "Targeted Interleukin 2 therapy enhances protective immunity induced by an autologous murine melanoma," <u>Cancer Res.</u> , 61(16):6178-84.	
C221	Nimtz et al., (1993) Structures of Sialylated Oligosaccharides of Human Erythropoietin Expressed in recombinant BHK-21 Cells," <u>Eur. J. Biochem.</u> , 213:39-56.	
C222	Pancook et al., (1996), "Eradication of established hepatic human neuroblastoma metastases in mice with severe combined immunodeficiency by antibody-targeted interleukin-2," <u>Cancer Immunol Immunother.</u> , 42(2):88-92.	
C223	Park et al., (2000), "Efficiency of promoter and cell line in high-level expression of erythropoietin," <u>Biotechnol. Appl. Biochem.</u> , 32:167-172.	
C224	Reisfeld et al., (1996), "Antibody-interleukin 2 fusion proteins: a new approach to cancer therapy," <u>J Clin Lab Anal.</u> , 10(3):160-6.	
C225	Reisfeld et al., (1996), "Involvement of B lymphocytes in the growth inhibition of human pulmonary melanoma metastases in athymic nu/nu mice by an antibody-lymphotoxin fusion protein," <u>Cancer Res.</u> , 56(8):1707-12.	
C226	Ruehlmann et al., (2001), "MIG (C1XCL9) chemokine gene therapy combines with antibody-cytokine fusion protein to suppress growth and dissemination of murine colon carcinoma," <u>Cancer Res.</u> , 61(23):8498-503.	
C227	Sabzevari et al., (1994), "A recombinant antibody-interleukin 2 fusion protein suppresses growth of hepatic human severe combined immunodeficiency mice," <u>Proc Natl Acad Sci USA</u> , 91(20):9626-30.	
C228	Seidenfeld et al., (2001), "Epoietin Treatment of Anemia Associated with Cancer Therapy: A Systematic Review and Meta-analysis of controlled Clinical Trials," <u>Journal of National Cancer Institute</u> , 93:1204-1214.	
C229	Shinkawa et al., (2003), "The Absence of Fucose but Not the Presence of Galactose or Bisecting N-Acetylglucosamine of Human IgG1 Complex-type Oligosaccharides Shows the Critical Role of Enhancing Antibody-dependent Cellular Cytotoxicity", <u>J. Biol. Chem.</u> , 278:3466-3473.	
C230	Spiekermann et al., (2002), "Receptor-mediated Immunoglobulin G Transport Across Mucosal Barriers in Adult Life: Functional Expression of FcRn in the Mammalian Lung," <u>J. Exp. Med.</u> , 196:303-310.	

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FORM PTO - 1449 SECOND SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT		ATTORNEY DOCKET NO.: LEX-011 APPLICANT(S): Gillies <i>et al.</i> SERIAL NO.: 09/780,668 EXAMINER: David A. Saunders FILING DATE: February 9, 2001 GROUP: 1644
EXAM. INIT.	OTHER DOCUMENTS: (Including Author, Title, Date, Relevant Pages, Place of Publication)	
	C231	Strom <i>et al.</i> , (1996), "Therapeutic Approach to Organ Transplantation", <u>Blackwell Science</u> , Chapter 36, pp. 451-456.
	C232	Syed <i>et al.</i> , (1998), "Efficiency of signaling through cytokine receptors depends critically on receptor orientation," <u>Nature</u> , 395:511-516.
	C233	Thommesen <i>et al.</i> , (2000), "Lysine 322 in the human IgG3 CH2 domain is crucial for antibody dependent complement activation", <u>Mol. Immunol.</u> , 37(16):995-1004.
	C234	Wells, (1990), "Additivity of Mutational Effect in Proteins," <u>Biochemistry</u> , 29(37):8509-8517.
	C235	Xiang <i>et al.</i> , (1998), "Induction of persistent tumor-protective immunity in mice cured of established colon carcinoma metastases," <u>Cancer Res.</u> , 58(17):3918-25.
	C236	Xiang <i>et al.</i> , (1999) "T Cell memory against colon carcinoma is long-lived in the absence of antigen," <u>J Immunol.</u> , 163(7):3676-83.
	C237	Xiang <i>et al.</i> , (2001), "A dual function DNA vaccine encoding carcinoembryonic antigen and CD40 ligand trimer induces T cell-mediated protective immunity against colon cancer in carcinoembryonic antigen-transgenic mice," <u>J Immunol.</u> , 167(8):4560-5.
	C238	Xiang <i>et al.</i> , (2001), "Protective immunity against human carcinoembryonic antigen (CEA) induced by an oral DNA vaccine in CEA-transgenic mice," <u>Clin Cancer Res.</u> , 7(3 Suppl):856s-864s.
	C239	Yu <i>et al.</i> , (1998), "Phase I Trial of a Human-Mouse Chimeric Anti-Disialoganglioside Monoclonal Antibody ch14.8 in Patients With Refractory Neuroblastoma and Osteosarcoma", <u>J. Clin. Oncol.</u> , 16:2169-80.
	C240	Zagozdzon <i>et al.</i> , (1999), "Potentiation of antitumor effect of IL-12 in combination with paclitaxel in murine melanoma model <i>in vivo</i> ," <u>International Journal of Molecular Medicine</u> , 4:645-648.

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EXAMINER	DATE CONSIDERED
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Examples

Example 1. Construction of antibody-IL-2 genes with substitutions of the Lys codon at the fusion junction

5 The amino acid sequence at the junction of the antibody-IL-2 fusion protein is SerProGlyLys-AlaProThr (SEQ ID NO: 1), in which the SerProGlyLys (SEQ ID No. 2) is the normal carboxy terminus of the heavy chain of the antibody, and AlaProThr is the N-terminal sequence of mature IL-2. In order to determine the effect alterations in the region of the fusion junction on the pharmacokinetics of the fusion protein, substitutions or deletion of the residue were made by mutagenesis, as described below.

A b
No A b insert found

The expression vector for immunocytokines was described in Gillies *et al.*, (1998) J. Immunol. 160:6195-6203. In the human gamma-1 gene encoding the heavy chain, the XmaI restriction site located 280 bp upstream of the translation stop codon was destroyed by introducing a silent mutation (TCC to TCA). Another silent mutation (TCT to TCC) was introduced to the Ser codon three residues upstream of the C-terminal lysine of the heavy chain to create the sequence TCC CCG GGT AAA (SEQ ID No. 3), which contains a new XmaI site [Lo *et al.*, (1998) Protein Engineering 11:495-500]. The IL-2 cDNA was constructed by chemical synthesis and it contains a new and unique PvuII restriction site [Gillies *et al.*, (1992) Proc. Natl. Acad. Sci. 89:1428-1432]. Both the XmaI and PvuII sites are unique in the expression vector, and they facilitated mutagenesis of the lysine codon which lies at the junction of the CH3 and the IL-2 DNA.

Substitution or deletion of the Lys codon was achieved by replacing the XmaI-PvuII fragment in the immunocytokine expression vector with an oligonucleotide duplex encoding the desired mutation. In this case the variable regions of the heavy and light chains were derived from the humanized KS antibody, which recognized a human antigen called EpCAM (Epithelial cell adhesion molecule). The sequences of the oligonucleotide duplexes used in the present invention are listed below, where the codons in bold encode the desired mutations, and the sequences in italics, CCCGG and CAG are the cohesive end of the XmaI site and the blunt end of the PvuII site, respectively. The